REMARKS

I. Status of Claims

Claims 25-28, 31-38 are pending in the application, among which claim 32 is withdrawn from consideration and the remaining claims are examined and rejected in the present Office Action.

By this amendment, Applicants have amended Claims 25 and 34 and added Claim 39.

II. Amendment of Claims

Applicants in the previous amendment amended Claims 25 and 34 to include a limitation regarding the relative amount of lactam in the composition after storage. Applicants by this amendment have amended Claim 34 to delete this limitation, amended Claim 25 to change this limitation to read "wherein after storage of the pharmaceutical composition in a sealed container at 45 °C for 4 weeks the amount of corresponding lactam that is formed in the pharmaceutical composition is less than 0.5% by weight relative to the initial amount of the 4-amino-3-substituted-butanoic acid derivative in the pharmaceutical composition," and added Claim 39 that includes a similar limitation as in the amended Claim 25. Support for this amendment can be found in the specification as filed, for example, page 6, lines 2-12, and Examples 1-3. No new matter has been added by this amendment.

III. Claim Rejection under 35 U.S.C. § 102

The Examiner has rejected Claims 25-27, 29, and 31 under 35 U.S.C. §102(b) as allegedly being anticipated by Woodruff (US 5,084,479). Applicants did not believe that the Examiner meant to reject Claim 29 as Claim 29 was cancelled by the previous amendment and, thus, is no longer pending in the application. Accordingly, Applicants do not address the rejection to Claim 29 here. As to the other claims, we note the Examiner's comment that "Although the reference is silent about 'wherein as compared with a second composition that the same compounds as the pharmaceutical composition. . . ,' such preamble to the claims gives no patentable weight to the claimed invention since the product is not dependent upon the manner in which is compared. Thus, Woodruff anticipates the claimed invention." Applicants believe that the language at issue further defines the claims and, therefore, should be considered in the

patentability determination. Nonetheless, to expedite the allowance of the claims Applicants have amended Claim 25 to change the language at issue to read: "wherein after storage of the pharmaceutical composition in a sealed container at 45 °C for two weeks the amount of corresponding lactam that is formed in the pharmaceutical composition is less than 0.5% by weight relative to the initial amount of the 4-amino-3-substituted-butanoic acid derivative in the pharmaceutical composition." The above language defines a limitation or the claimed invention and, therefore, should be considered in the patentability determination. As the Examiner admitted, Woodruff is silent about the relative lactam content in the composition as compared with a corresponding composition without the α amino acid. It does not even mention the existence or amount of lactam in the solution. Accordingly, Woodruff does not anticipate Claims 25 as amended. Claims 26, 27, and 31 depend from claim 25 and, therefore, are anticipated by Woodruff either.

IV. Claim Rejection under 35 U.S.C. §103

Claims 25-28, 31, and 33-38 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Jao et al. (US 5,660,861) in view of Robson et al. (US 4,126,684), and further in view of Costa et al. (US 5,248,678) and Bays et al. (WO 96/11690). Claims 25-28, 31, and 33-38 are drawn to a pharmaceutical composition comprising an α amino acid and gabapentin or pregabalin. Claims 25-8, 31, and 33 further recite that the composition is a liquid and Claims 34-38 further recited that the composition is a solid. Applicants respectfully submit that, for reasons of record and further reasons detailed below, the Examiner has not met his burden of establishing a *prima facie* case of obviousness (MPEP §2143) and, therefore, the rejection is improper.

A. The References Provide No Motivation

Applicants respectfully submit that the Examiner's allegation of motivation to modify the references or combine the reference teachings is not supported by the references. (MPEP 2143.01) The claimed invention relates to a pharmaceutical composition comprising an α amino acid and gabapentin or pregabalin. According to the Examiner, Jao et al. disclose a dosage form for delivering an antiepileptic drug such as gabapentin and method of making the dosage form, wherein said active ingredient is formulated with secondary ingredients such as sorbitol. The Examiner admitted that Jao et al. do not teach the inclusion of an alpha amino acid, nor the

specific amount of the alpha amino acid in the composition. To remedy the defect of Jao et al., the Examiner cited Robson et al. as disclosing a composition comprising "baclofen, alpha amino acid such as glycine, auxiliary agent (i.e., sorbitol, mannitol, lactose, etc . . . " The Examiner goes on to conclude:

> one of ordinary skill in the art would have been motivated to "include a neutral amino acid such as glycine in the composition of Jao for the advantage of providing a delivery system that would deliver the drug formulation in continuous-release dose for predictable and improved therapy (Jao: col. 3, lines 20-25) since both Jao and Robson disclose a pharmaceutical excepient such as sorbitol and a drug that is a 4-amino-3-substituted-butanoic acid derivative (Jao: col. 6, lines 52-67, and col. 7, lines 42-52; Robson: col. 2, lines 5-8, and col. 3, lines 54-59)."

Applicants respectfully submit that, contrary to the Examiner's assertion, the alleged "advantage of providing a delivery system that would deliver the drug formulation in continuous-release dose for predictable and improved therapy" does not provide motivation to include a neutral amino acid such as glycine in the composition of Jao et al. Neither reference teaches that a neutral amino acid such as glycine would contribute to the delivery system that would deliver the drug formulation in continuous-release dose for predictable and improved therapy as disclosed by Jao et al; nor has the Examiner pointed to any place in the references for such teaching. The language of Jao et al. refereed to by the Examiner (i.e., Jao: col. 3, lines 20-25) is merely a general statement about an "object of the present invention" of Jao et al., which provides no teaching at all as to whether or not an alpha amino acid would contribute to the achievement of that object. Without the teaching that an alpha amino acid would contribute to such as delivery system, a person skilled in the art would have no reason to include an alpha amino acid to the composition of Jao et al. in order to achieve the alleged advantage. Moreover, since the composition of Jao et al. allegedly already has the "advantage of providing a delivery system that would deliver the drug formulation in continuous-release dose for predictable and improved therapy," it would be against logic and scientific wisdom to modify the composition of Jao et al. in order to achieve the same advantage. Rather, because the composition of Jao et al. allegedly already has the alleged advantage and because neither reference teaches that an alpha

amino acid contributes to such an advantage, a person skilled in the art would be discouraged to make the modification proposed by the Examiner.

Similarly, Applicants respectfully submit that Examiner's stated reason "[since] both Jao and Robson allegedly disclose a pharmaceutical excipient such as sorbitol and a drug that is 4-amino-3-substituted-butanoic acid derivative" does not support the alleged motivation to include an alpha amino acid in the composition of Jao et al. The mere disclosure that sorbitol might be used in a formulation of 4-amino-3-substituted-butanoic acid does not suggest in any way the inclusion in the formulation an alpha amino acid, which has different chemical structure and properties from sorbitol. As admitted by the Examiner, Jao et al. do not teach the inclusion of an alpha amino acid in the composition. Robson mentioned more than thirty "pharmaceutical excipients" that might be used in the invention disclosed therein (See, e.g., col. 3, lines 54-67). However, it provides no guidance on the selection of any particular excipients. Thus, the references at best represent an "obvious to try" rationale, which is not a proper basis for the obviousness rejection.

The Examiner has further alleged that "since the equivalence of gabapentin and baclofen as GABA agonist is well known in the art, the selection of any known GABA agonists from limited examples of Costa to arrive as the claimed invention would be within the level of ordinary skill in the art." Applicants submit, however, that even if Costa allegedly shows that gabapentin and beclofen are functional equivalent as GABA agonists, modifying the composition of Jao et al. by selection of any known "GABA agonists from the limited examples of Costa" still can not arrive at the claimed invention that comprises an alpha amino acid in addition to the active agent. Nor does the alleged functional equivalence of gabapentin and beclofen as GABA agonist support a motivation to modify Robson et al. by selection of any known "GABA agonists" from the limited examples of Costa. As noted in Applicants' reply to the previous Office Action, Robson et al. relate to a composition that includes an addicting agent and baclofen. The intended purpose of combining baclofen with the addicting agents in the composition is to prevent future addiction or to ameliorate the withdrawal symptoms in the addicted. (See Robson, et al., column 1, lines 29-34). The basis for including baclofen in the composition is the property that "4-amino-3-p-halophenylbutyric acids and derivatives, especially baclofen . . . actually depress the symptoms of withdrawal of addicting agents and reduces the

craving for the addicting agents. . . ". (See Robson et al., column 1, lines 21-33). Robson et al. do not teach that gabapentin has this property. To the contrary, Robson et al. suggest that gabapentin is not expected to have this property when they disclose that the above property of baclofen was "surprisingly" found. (See Robson et al., column 1, lines 21-33). Nor does Robson et al. teach any desirability to include gabapentin in the composition for the intended purpose of preventing future addiction or ameliorating the withdrawal symptoms in the addicted. Therefore, a person skilled in the art would not be motivated to modify the composition of Robson et al. by including gabapentin or substituting baclofen with gabapentin in the composition of Jao et al. to arrive at the claimed invention.

The Examiner has applied the "analogous art" test to support his conclusion of motivation, stating that one would have been motivated to combine the references and make the modification "because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about." At the outset, Applicants respectfully submit that the mere finding that cited references meet the "analogous art" test is not a proper basis for concluding that a skilled artisan would have been motivated to combine references; rather, the "analogous art" test only begins the inquiry into whether a skilled artisan would have been motivated to combine references. In re Kahn, 78 USPQ2d 1329 (CAFC 2006). Moreover, contrary to the Examiner's assertion, Applicants believe that the cited references are not pertinent to the problem that concerns the Applicants. As disclosed in the specification, one particular problem with which Applicants were concerned is degradation of gabapentin into toxic corresponding lactam in a finished product (see, for example, "Background of the Invention"). Applicants have made earnest studies to solve the problem and have found that the degradation of gabapentin can be prevented by addition of an alpha amino acid (see "Summary of the Invention"). None of the cited references is concerned with the degradation or stability of the active agent in the composition or of the composition itself. Because none of the reference teaches that an alpha amino acid would stabilize the composition containing a 4-amino-3-substituted butanoic acid derivative, a person skilled in the art, possessed with the understandings and knowledge reflected in the references, and faced with the problem facing the Applicants, would not be motivated to modify Jao et al. to arrive at the claimed invention. In re Kahn, 78 USPQ2d 1329 (CAFC 2006).

Moreover, there is a further reason that there is lack of motivation to modify the reference to arrive at the invention as claimed in Claims 25-28, 31, and 33. As noted above, Claims 25-28, 31, and 33 are drawn to a liquid composition, while Jao et al. relate to a solid one. To arrive at the claimed invention, the proposed modification not only requires the inclusion of an alpha amino acid, but also requires changing the form of the composition of Jao et al. from a solid to a liquid. Applicants respectfully submit that proposed modification would render the composition of Jao et al. inoperable for its intended purpose; therefore, there is no suggestion or motivation to make the modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP 2143.01. Jao et al. disclose that conventional dosage forms for epileptic drugs prior to the invention of Jao et al. produce undesirable peaks and valley patterns and do not provide for dosage-regulated drug therapy over an extended period of time. (Jao et al., Col. 2, lines 13-25) One of the intended purposes of the invention of Jao et al. was to provide a dosage form that overcomes these shortcomings of the prior art dosage forms by providing controlled delivery of the drug over an extended period of time. (See, e.g., col. 2, lines 57 -67; col. 3, lines 1-25). The composition of Jao et al. requires a solid dosage form and maintaining the integrity of the dosage form. (See Abstract). The dosage form comprises discrete structures, such as "wall," (See, e.g., col. 5, lines 5, 35, 49, 60), "layers," (See, e.g., col. 5, line 57; col. 7, line 66); "compartment" (See, e.g, col. 5, lines 30; col. 7, lines 24; col. 8, lines 40). Each structural feature serves a specific function. For example, Jao et al. specifically emphasize that the "wall 12 does not lose its structure" during the dispensing of antiepileptic drug (col. 5, lines 41-43) and that the "dual walls 12 and 27 provides unexpected advantages as wall 12 and wall 27 in combination protect a hydroscopic antiepileptic drug 15 from the unwanted influences of aqueous and biological fluids, they shield an antiepileptic drug 15 from converting from a soluble to an insoluble antiepileptic drug 15 in the gastrointestinal pH range of 1 to 8." (Col. 8, lines 53-60). Therefore, the structural features are essential for the intended purpose of the composition of Jao et al. The proposed modification of the composition of Jao et al. (i.e. to change it to a liquid), requires complete destruction of the essential structural features of the composition of Jao et al., which, consequently, will render the composition of Jao et al. totally inoperable.

In addition, Applicants submit that the proposed modification would also change the mode of operation of the composition of Jao et al. Jao et al. teach that the dosage form delivers

an antiepileptic drug "by a process selected from the group consisting of osmotic, diffusion, bioerosion and ion-exchange." (See, e.g., col. 3, lines 1-4 and 41-47). None of these delivery processes is relied on by the claimed invention. Therefore, changing the solid dosage form of Jao et al. to a liquid would necessarily change the delivery process that the solid dosage form of Jao et al. was designed to utilize. And as such, the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP 2143.02.

The Examiner has admitted that the modified teaching of Jao et al. in view of Robson et al. and Costa et al., does not teach the element recited in Claims 25-28, 31, and 33 that the composition is a liquid. To remedy this defect, the Examiner cited Bays et al., allegedly "to demonstrate routine knowledge in preparing 4-amino-3-substituted-butanoic acid derivative (i.e, gabapentin) in various dosage forms including solid or liquid dosage form." Applicants respectfully submit that the mere teaching that a 4-amino-3-substituted-butanoic acid derivative may be prepared in solid or liquid dosage forms would provide no motivation to make the proposed modification as reasons set forth above.

B. The References Provide No Reasonable Expectation of Success

Applicants believe that there is no reasonable expectation of success, to modify Jao et al. to arrive at the claimed invention. In determining obviousness the Examiner is required to consider the claimed invention as a whole, which in turn requires looking not only to the subject matter which is literally recited in the claim in question "but also to those properties of the subject matter which are inherent in the subject matter and are disclosed in the specification." *In re Antonie*, 559 F.2d 618, 619, 195 U.S.P.Q. 6, 8 (C.C.P.A. 1977). Applicants have disclosed in the specification that the claimed invention possesses superior storage stability. Specifically, the specification discloses that pharmaceutical preparations containing gabapentin is difficult to prepare because the active ingredient readily undergoes degradation to form corresponding lactam and that it is necessary in manufacturing a pharmaceutical preparation of gabapentin to prevent the formation of the lactam. (See "Background of the Invention"). The comparative data disclosed in the Examples show that addition of alpha amino acid to the composition reduced the formation of the corresponding lactam, thus stabilizing the composition. The stability of the claimed composition is a property inherent in the claimed invention and is disclosed in the

specification. Therefore, the stability is part of the claimed invention as a whole and therefore should be considered in determining whether or not the claimed invention is obviousness. As explained above, none of the cited references suggest that an alpha amino acid would stabilize the composition containing gabapentin or pregabalin. Therefore, a person skilled in the art in vie of the references would not have a reasonable expectation of success to do what Applicants have done.

Further, with respect to Claims 25-28, 31 and 33, which are drawn to a liquid composition, as explained above, the proposed modification would also require the destruction of the essential structures and change of the delivery process of the solid composition of Jao et al. a person skilled would not have reasonably expected that the proposed modification would be successful.

C. The References Do Not Suggest All Claim Limitations.

Applicants submit that the cited references do not suggest all the limitations of the claims. For example, Claim 25 as amended and new Claim 39 recite a limitation that after storage of the pharmaceutical composition in a sealed container at 45 °C for two weeks the amount of corresponding lactam that is formed in the composition is less than 0.5% by weight relative to the initial amount of the 4-amino-3-substituted-butanoic acid derivative in the composition. This limitation is not suggested by any of the reference.

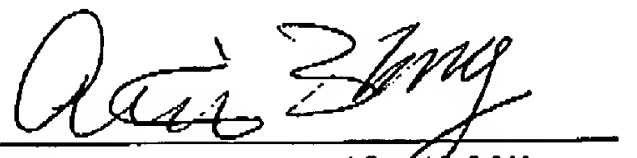
V. Double Patenting

The Examiner has maintained the rejection to Claims 25-31 and 33 under the judicially created doctrine of double patenting over claims 28-39 of co-pending US Application No. 09/674,819. Applicants submitted in the previous reply that the rejection is improper because US Application No. 09/674,819 has not yet issued as patent and no actual double patenting rejection may be properly made over claims of a co-pending application. (MPEP 804). Applicants respectfully reiterate this argument and submit that the rejection should be withdrawn.

VI. Concluding Remarks

In view of the amendments and the foregoing remarks, Applicants respectfully request reconsideration of the matter, the withdrawal of all the rejections, and timely issuance of a Notice of Allowance.

Respectfully submitted,



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